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MEMORANDUM

TO: Gary Patterson
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DATE: May 1, 2003

SUBJECT: Response to Comments from Methyl Bromide Subchronic Regulatory Level
Workshop on February 26, 2003

The Department conducted a workshop on February 26, 2003 to discuss the regulatory levels for human subchronic exposure to methyl bromide. The Medical Toxicology Branch staff recommended levels were 16 ppb for adults and 9 ppb for children based on the lack of proprioceptive-placing response in dogs with a No-Observed-Effect-Level (NOEL) of 5 ppm (Schaefer, 2002). The previous proposed levels were 2 ppb for adults and 1 ppb for children based on decreased activity in dogs with an estimated NOEL of 0.5 ppm (Newton, 1994) in the Methyl Bromide Risk Characterization Document (RCD) for Inhalation Exposure (DPR, 2002). The revised recommended levels were made available to all interested parties as an addendum to the RCD (DPR, 2003). Both oral and written comments were received at and subsequent to the workshop (in Appendix A of this memorandum). Four issues were identified:

- A. The quality and selection of the NOEL for the Schaefer study (Schaefer, 2002).
- B. The NOEL for the determination of the subchronic regulatory level.
- C. The exposure to chloropicrin from products containing methyl bromide and chloropicrin.
- D. The potential increased sensitivity by children and people with illnesses such as multiple chemical sensitivity and asthma.

This memorandum is a response to submitted comments and addresses the issues identified in the comments instead of individual submissions since the same issues appeared in more than one of the submissions. It also included comments from Dr. Virginia Moser¹ (U.S. Environmental Protection Agency, U.S. EPA), as an external reviewer for DPR, on the Schaefer and Newton studies (Appendix B). After consideration of the submitted comments and Dr. Moser's review, DPR concluded that the weight of the evidence supported the derivation of subchronic regulatory levels from the reference concentrations from three key studies (Newton, 1994; Schaefer, 2002; and Norris *et al.*, 1993). The recommended regulatory levels are 16 ppb for adults and 9 ppb for children proposed previously in the Addendum using 5 ppm as the NOEL from the Schaefer study (DPR 2003).

¹ The Methyl Bromide Industry Panel has recommended the review of the Schaefer study by Dr. Moser. Dr. Moser is a well-known expert on neurotoxicity and a brief summary of her expertise is included in Appendix B.



A. The quality and selection of the NOEL for the Schaefer study

1. In the submitted comments, two NOELs, 20 ppm and less than 5 ppm, were discussed for the Schaefer study.
 - Comments from the AMBI indicated that the NOEL should be 20 ppm because the observations showed no clear dose-response relationships, a lack of persistence of effect, no consistency between genders, and were not corroborated with other findings.
 - Comments from OEHHA (March 11, 2003 memorandum) did not propose a NOEL for this study but implied that the NOEL should be less than 5 ppm by the statement that the results of the Schaefer study support the selection of 5 ppm from the Newton study as the LOAEL. The memorandum focused mainly on concerns regarding the experimental design of the study because it did not follow U.S. EPA Federal Insecticide Fungicide and Rodenticide Act (FIFRA) guidelines for a 13-week subchronic neurotoxicity study. In particular, OEHHA was concerned that the number of animals, dose selection and intervals, and the duration of the exposure were not the same as those in the guidelines.
2. Dr. Moser commented that the study design was reasonable with adequate opportunities to detect neurobehavioral or toxicological changes (Appendix B). She concluded that the NOEL for the study should be 10 ppm based on several effects (soft, mucoid feces, and/or diarrhea; eye discharge; and lack of visual placing response) at 20 ppm (Table 1). She considered the finding of proprioceptive placing response, or more correctly visual placing response, alone not to be sufficient to use as a critical effect for the study because of the low incidence and lack of correlative changes. With regard to the one dog diagnosed with idiopathic febrile necrotizing arteritis, she concluded that the effects observed in this dog were not related to methyl bromide treatment.
3. A NOEL of 5 to 10 ppm was recommended by DPR external reviewers (J. Last and K. Pinkerton, University of California) (DPR, 2003).
4. In comparison, DPR selected 5 ppm as the NOEL for the study in the Addendum.
 - The difference in opinions about the NOEL was primarily due to differences regarding the strength of evidence needed to establish the study NOEL. DPR believed that the strength of evidence to identify a chemical as a neurotoxicant should be different (i.e. more evidence) than that to define a NOEL for the neurotoxicity. For the identification of a neurotoxicant, the experiments are generally conducted with doses over a wide range (i.e. 100-fold) and include a high dose that would result in overt toxicity. It is then reasonable to use the criteria indicated by AMBI to clearly demonstrate if a chemical is a neurotoxicant. For a known

neurotoxicant, DPR believed that limited evidence was sufficient to determine the study NOEL for use in risk assessment. When the experiments are conducted within narrow dose ranges (i.e. 4-fold as in the Schaefer study) close to the actual NOEL for the effect and with a limited number of animals, it is unlikely that a clear dose-response can always be demonstrated. Individual and gender variations in response may be more evident at these low doses.

- DPR considered the OEHHHA concerns on the protocol invalid in that the study was a special study designed for the purpose of defining a NOEL as recommended by the National Research Council (NRC)², and not as a submission to fill a data requirement for pesticide registration. Therefore, the doses were selected to bracket the expected NOEL in order to clarify the effects at the low dose region. The number of dogs used (4/sex/group) was consistent with the FIFRA guidelines for the use of dogs in toxicity (chronic) studies. DPR considered it inappropriate to use the requirement for rats (10 animals per sex per group) as a basis for comparison. In addition, the duration of exposure was specifically tested for 6 weeks, instead of 13 weeks, because it reflected potential human exposure duration based on DPR analysis of the air monitoring data and use data.
- In comparison to AMBI and Dr. Moser, DPR considered the lack of proprioceptive response at 10 ppm and 20 ppm as treatment-related because dogs prior to treatment, and the control dogs during the experiment, did not show this deficit. A dose-response relationship was demonstrated since the incidences increased from 0/8 in the control and 5 ppm groups to 1/8 in the 10-ppm group, and to 2/8 in the 20 ppm group (Table 1). With only eight dogs (4 males and 4 females) per group, the lack of statistical significance in these incidences could be expected. Since low doses were selected to clearly identify a NOEL and the dose range was only 4-fold, the change in severity of the effect with increasing doses was expected to be minimal. The effect was persistent in that the 20 ppm male dog showed the deficit at three consecutive testing periods (weeks 2, 4, and 6). The apparent lack of persistence for the male dog at the lower dose of 10 ppm, may be a reflection of the effect being more transient at 10 ppm and more persistent at 20 ppm. This could also be the case for the one female at 20 ppm, which was affected only on week 2. DPR did not consider these results as evidence of a lack of consistency between male and female. Variation in response is expected when the doses are only 2-fold apart and only 4 animals are used per gender. Therefore, this type of variation is not a valid reason to discount the observation.
- DPR considered the effects (tremor and twitching) observed in one dog at 5 ppm as an insufficient basis to determine the NOEL. While these effects might be consistent with the

² DPR requested the National Research Council to review the draft Risk Characterization Document (NRC, 2000). The NRC had recommended a new study to be conducted because they considered the effects observed at 5 ppm in the Newton study as equivocal.

neurotoxicity of methyl bromide, they were noted only in one dog at the lowest dose, not at the higher doses. In addition, the response in this dog might be confounded by symptoms associated with the idiopathic febrile necrotizing arteritis (sick beagle syndrome), diagnosed by veterinarians. This conclusion is consistent with Dr. Moser's view that the effects observed in this dog were not due to treatment (Appendix B).

B. The critical NOEL for the determination of the subchronic regulatory level

1. In the submitted comments, two critical NOELs³ were proposed for the calculation of the regulatory levels. The differences on the critical NOEL can be attributed to differences in opinion on the NOEL for the Schaefer study (as discussed previously) and how other studies in the database are considered.

- Most of the AMBI submitted comments compared only the Schaefer and Newton studies and concluded that the Schaefer study (with the NOEL at 20 ppm) should be used to calculate the regulatory level because it was considered a better conducted study. V. Piccirillo (AMBI) provided the only comment related to the magnitude of the critical NOEL. He noted that the exposure levels used in the Schaefer study were within the range of the NOELs seen from other studies, and that the inhalation NOEL for subchronic exposure would be in the range of 5 ppm to 20 ppm.
- On the other hand, OEHHA (March 11, 2003 memorandum) commented that the critical NOEL should be at 0.5 ppm because the result from the Newton study remained valid and the finding (decreased responsiveness) had the lowest NOEL compared to other endpoints. OEHHA further commented that the estimated NOEL was supported by the Schaefer study NOEL (implied at 0.5 ppm) and agreed well with other studies in a variety of species. No discussion was provided on how the comparison with other studies was made. In a subsequent memorandum (April 9, 2003), OEHHA reiterated their position and that their recommendation of 1 ppb and 2 ppb for the regulatory levels were consistent with those made by the NRC.

2. Dr. Moser commented that the dose-response in the Schaefer study (with a NOEL of 10 ppm) was supported by the Newton study. She noted that dogs exposed to methyl bromide from 50 ppm to 150 ppm showed clear neurotoxicity in the Newton study (Table 2). These comments implied that the NOEL for the Newton study was at 5 ppm.

³ It should be noted there is a distinction between a study NOEL and a critical NOEL. The study NOEL defines the no-effect level for a particular effect or effects from a toxicity study. Different NOELs may be derived for different endpoints, or for the same endpoint from different studies. A critical NOEL is derived from the study NOELs using a weight of evidence approach. It is used to calculate the risk (margin of exposure) from a particular effect of concern, in this case neurotoxicity, associated with a certain exposure duration (i.e. acute, subchronic, and chronic).

3. Dr. J. Last (University of California) as a reviewer for DPR, recommended the use of 5 ppm to develop the regulatory levels.

4. DPR had considered the estimated NOEL of 0.5 ppm from the Newton study as the critical NOEL in the Risk Characterization Document. However with the submission of the Schaefer study and external reviews of the Schaefer and Newton studies, DPR concluded that the weight of evidence supported the use of 5 ppm as the critical NOEL to evaluate neurotoxicity after subchronic exposure to methyl bromide (Table 4). DPR identified three key studies in the determination of the critical NOEL: Newton study (decreased activity in dogs, Lowest-Observed-Effect-Level, LOEL of 5 ppm); Schaefer study (lack of proprioceptive placing response, NOEL of 5 ppm); and Norris *et al* study (decreased brain weight in rats, LOEL of 30 ppm). The recommended regulatory levels are, therefore, 16 ppb for adults and 9 ppb for children (Table 5) as proposed previously in the Addendum using 5 ppm as the NOEL from the Schaefer study (DPR 2003).

- In the Newton study, the NOEL (0.5 ppm) was estimated because the lowest dose, 5 ppm, was the LOEL for the study. At 5 ppm, two of 8 dogs showed decreased responsiveness at the end of 6 weeks of exposure (Table 2). No other effects were observed. In the RCD, a default uncertainty factor of 10-fold was used to derive the estimated NOEL of 0.5 ppm because there were no data to determine the appropriate factor for the extrapolation. While the NRC concurred with the DPR's selection of 0.5 ppm as the critical NOEL, it should be emphasized that the NRC expressed both concerns and reservations about the findings. In their discussions of the data, the NRC noted that the finding at the LOEL of 5 ppm was equivocal because of the lack of a dose-response curve, the subjectiveness of the observation, and the low number of animal studied. The NRC recommended a new study be conducted to verify the neurotoxicity endpoints of decreased responsiveness at 5 ppm. At the same time, the NRC considered it reasonable to use the observation as a conservative endpoint because of neurotoxicity observed in humans and the potential long-term neurological effects.
- From the results in the Schaefer study and Dr. Moser's comments, DPR concluded that 5 ppm was the actual NOEL for methyl bromide neurotoxicity after subchronic exposure. Since the Schaefer study was a better conducted study and more clearly defined the NOEL for neurotoxicity, DPR believed that more weight should be placed on the finding from this study in the weight of evidence considerations.
- In a rat neurotoxicity study, reduced brain weight was observed at all doses with a LOEL of 30 ppm and an estimated NOEL of 3 ppm (Norris *et al.*, 1993; Table 3). As stated in the U.S. EPA Neurotoxicity Guidelines, the reduction of absolute brain weight is an adverse effect in itself. This effect should not be dismissed in the presence of reduced body weight because brain weight is generally unaffected by body weight changes.

- These recommended regulatory levels are at the low end of the range of reference concentrations: 16 to 31 ppb for adults and 9 to 18 ppb for children based on the NOELs supported by a majority of the reviewers (bolded values in Table 4). The use of the low end values represents a health-protective approach given the differences in opinion regarding the adversity of the effects and the NOELs for the Newton and Schaefer studies. While these values are derived from a NOEL of 5 ppm from the Schaefer study, they are the same as those from the Newton study using 5 ppm as the NOEL. Furthermore, the use of these values provides protection for the brain weight reduction effect observed in the rat neurotoxicity study (Norris *et al.*, 1993) with reference concentrations of 20 ppb and 11 ppb for adults and children (Table 4).
- These recommended levels are consistent with established regulatory levels for other durations. The DPR acute, 1-week, and chronic inhalation exposure regulatory levels (adults/children) are 210 ppb /250 ppb, 120 ppb/70 ppb, and 2 ppb/1 ppb, respectively (Table 5). The subchronic levels are more than 10-fold lower than those for acute exposure, about 10-fold lower than those for 1-week exposure, but about 10-fold higher than that for chronic exposure (annual). The previously proposed subchronic levels (2 ppb /1 ppb) are the same as the chronic exposure level. These regulatory levels are also between the range of Reference Exposure Levels determined by OEHHA for 1 hour and chronic exposures. The 1 hour RELs for mild and severe effects are 1 ppm and 5 ppm, respectively, and the chronic REL is 1 ppb. OEHHA is in the process of reevaluating these values to specifically address infant and children exposure. The U.S. EPA chronic reference concentration is also at 1 ppb.
- These levels are higher than those recommended in the RCD based on the Newton study and reviewed by the NRC. While the NRC had agreed with DPR 's previously proposed regulatory levels of 1 ppb and 2 ppb, the NRC has not been asked to re-evaluate these levels in light of the Schaefer study, a study conducted under the recommendation of the NRC. Dr. J. Chambers, a member of the NRC who reviewed the RCD, has recommended the use of 20 ppm from the Schaefer study as the critical NOEL to calculate the regulatory levels (DPR, 2003).

C. The exposure to chloropicrin from products containing methyl bromide and chloropicrin

Since methyl bromide is used in combination with chloropicrin, DPR agreed with the comments that there might be potential exposure to chloropicrin. However, there are no toxicity studies that exposed experimental animals to both compounds simultaneously. Thus, the potential toxicity can not be quantitatively determined at this time. There is also a lack of chloropicrin air monitoring data but the Air Resources Board has conducted monitoring with the report pending. DPR has prioritized chloropicrin for risk assessment. Nevertheless, DPR recommends that

regulations on methyl bromide need to consider the potential exposure to chloropicrin when products containing both methyl bromide and chloropicrin are used.

D. The potential increased sensitivity by children and people with illnesses such as multiple chemical sensitivity or asthma

1. DPR agreed with the comments that there may be potential increased sensitivity by children and those with illnesses. DPR already addressed the concern about exposure of children by calculating child specific regulatory levels (lower regulatory level) using the higher breathing rate for children than that for adults. In addition, the DPR acute regulatory level is based on developmental toxicity in fetal rabbits to address potential fetal toxicity in human after methyl bromide exposure. A developmental neurotoxicity study can be useful to evaluate the adequacy of these approaches. However, at this time, U.S. EPA requires such a study type only for organophosphate pesticides.

2. With respect to the additional uncertainty factor as mandated under the Food Quality Protection Act, the NRC indicated that such a factor was not necessary since the critical NOELs for various exposure scenarios selected by DPR in the RCD were "quite conservative." With the revision of the subchronic regulatory level, DPR does not recommend the use of an additional uncertainty factor because the effects used to determine the critical NOEL can be considered conservative. In the Schaefer study, the DPR LOEL of 10 ppm showed only 1 dog (1/8 dogs) with a lack of proprioceptive placing response and only on weeks 2 and 4, but not on week 6 (Table 1). There were no other treatment-related effects in the study. Dr. Moser did not consider this single finding at 10 ppm to be sufficient basis for the LOEL and considered this dose as the NOEL. Both Dr. Chambers and the Dr. Schaefer, the study director, had set the NOEL at even a higher dose of 20 ppm.

3. DPR agreed with the comments that people with multiple chemical sensitivity or asthma might have increased sensitivity to methyl bromide since inhalation is the primary route of exposure. However, DPR is unaware of any data or experimental animal model, which can be used to quantify this potential increased sensitivity to methyl bromide. DPR has incorporated a default 10-fold uncertainty factor generally used, in the absence of data, to account for variations between individuals in the population due to physiological or other potential factors.

Table 1. Effects in dogs in the Schaefer study.^a

| Effects | Methyl bromide concentration (ppm) | | | | | | | |
|--|------------------------------------|-----|------------|------------|---------|-----|-----|------------|
| | Males | | | | Females | | | |
| | 0 | 5 | 10 | 20 | 0 | 5 | 10 | 20 |
| Lack of proprioceptive placing response | | | | | | | | |
| -2 week | 0/4 | 0/4 | 0/4 | 0/4 | 0/4 | 0/4 | 0/4 | 0/4 |
| -1 week | 0/4 | 0/4 | 0/4 | 0/4 | 0/4 | 0/4 | 0/4 | 0/4 |
| week 2 | 0/4 | 0/4 | 1/4(#8732) | 1/4(#8723) | 0/4 | 0/4 | 0/4 | 1/4(#8751) |
| week 4 | 0/4 | 0/4 | 1/4(#8732) | 1/4(#8723) | 0/4 | 0/4 | 0/4 | 0/4 |
| week 6 | 0/4 | 0/4 | 0/4 | 1/4(#8723) | 0/4 | 0/4 | 0/4 | 0/4 |
| Feces Findings^b | | | | | | | | |
| Total occurrences | 6 | 4 | 21 | 45 | 8 | 6 | 8 | 15 |
| # Dogs involved | 2 | 2 | 4 | 4 | 2 | 2 | 1 | 3 |
| Eye Discharge^b | | | | | | | | |
| Total occurrences | 0 | 0 | 0 | 82 | 76 | 33 | 3 | 14 |
| # Dogs involved | 0 | 0 | 0 | 2 | 2 | 1 | 2 | 3 |

^{a/} Data from Schaefer, 2002. Incidence = number of dogs affected/number examined for proprioceptive placing, the dog identification number (#) is noted in the parenthesis.

^{b/} Analysis from Dr. Moser (Appendix B).

Table 2. The neurotoxicity of methyl bromide in dogs in the Newton study.^a

| Concentrations ppm | Onset | Clinical Signs and Incidences ^c | Clinical Signs with Additional Exposure |
|---------------------|-----------------|--|---|
| 158± 7 ^b | Day 2 | Decreased activity (8/8) | Severe neurotoxicity, cerebellar lesions (8/8) |
| 103± 9 | Day 9 | Decreased activity (3/8) | Day 9 to 10: emesis (1/8), tremor (1/8), decreased activity (3/8); week 5: cerebellar lesions (1/8) |
| 53± 4 | Day 14 | Decreased activity (2/8) | |
| 26± 1 | 23-24 exposures | No effects observed | |
| 5± 0.4 | 30 exposures | Decreased responsiveness (2/8) | |

^{a/} Data from Newton, 1994.

^{b/} The dogs were exposed to 11 ppm for 24 exposure days, then 158 ppm for 6 exposure days.

^{c/} Incidences as number of dogs affected/total are shown in parentheses.

Table 3. The neurotoxicity of methyl bromide in rats exposed for 13 weeks.^a

| Effects | Males | | | | Females | | | |
|------------------|-------|-----------------|----------------|------------------|---------|------------------|------------------|------------------|
| | 0 | 30 | 70 | 140 | 0 | 30 | 70 | 140 |
| Brain weight (g) | 2.301 | 2.346 (102%) | 2.285 (99%) | 2.154** (94%) | 2.146 | 2.057** (96%) | 2.038** (95%) | 1.934** (90%) |
| Motor activity | | | | | | | | |
| 4 week | 1350 | 1614 | 1590 | 1509 | 1721 | 1828 | 1677 | 1460 |
| 8 week | 1551 | 1787 | 1500 | 1495 | 1684 | 1756 | 1353 | 1411 |
| 13 week | 1501 | 1402 | 1508 | 1438 | 1517 | 1627 | 1099** | 1159** |

^{a/} Data from Norris *et al.* (1993). n=10, ** significantly different from control group (p<0.01). Motor activity =mean cumulative test session counts.

Table 4. Reference concentrations for methyl bromide subchronic toxicity.

| Studies | Species/ Duration | Effect | NOEL/ LOEL (ppm) | ENEL ^a (ppm) | Human Equivalent NOEL ^b | | Reference concentration ^c | |
|----------------------------------|----------------------|--|------------------------|----------------------------|---------------------------------------|----------|---|--------|
| | | | | | Adult | Child | Adult | Child |
| Subchronic Exposure (6-13 weeks) | | | | | | | | |
| Newton, 1994 | Dog /6 weeks | Unrespon- siveness | <5 / 5 | 0.5 UF=10 | 0.16 ppm | 0.09 ppm | 2 ppb | 1 ppb |
| | | | | 1.7 UF=3 | 0.53 ppm | 0.30 ppm | 5 ppb | 3 ppb |
| | | | 5/ 50 | NA | 1.6 ppm | 0.9 ppm | 16 ppb | 9 ppb |
| Schaefer, 2002 | Dog/6 weeks | Tremors, twitching | <5/5 | 1.7 UF=3 | 0.53 ppm | 0.30 ppm | 5 ppb | 3 ppb |
| | | Absence of Proprio- ceptive placing response | 5 / 10 | NA | 1.56 ppm | 0.88 ppm | 16 ppb | 9 ppb |
| | | Feces findings, eye discharge, and lack of visual placing response | 10/ 20 | NA | 3.12 ppm | 1.78 ppm | 31 ppb | 18 ppb |
| | | No Effects | 20/ >20 | NA | 6.25 ppm | 3.53 ppm | 63 ppb | 36 ppb |
| Norris <i>et al.</i> , 1993 | Rat/ 13 weeks | Brain weight reduction | <30/30 | 3 UF=10 | 1.98 ppm | 1.12 ppm | 20 ppb | 11 ppb |

^{a/} In the absence of a No-Observed-Effect Level (NOEL), the Lowest-Observed-Effect Level (LOEL) is divided by an uncertainty factor (UF) to estimate a NOEL. The default UF may be 3 or 10-fold depending on the severity of the effect.

^{b/} Human equivalent NOELs take into consideration of respiratory rate differences between experimental animals and humans (based on children rate of 0.46 m³/kg/day and adult respiration rate of 0.26 m³/kg/day) and amortized for 24 hours of exposure. The default respiration rates for dogs and rats are 0.39 m³/kg/day and 0.96 m³/kg/day, respectively. For example, the calculation for adult human equivalent NOEL based on the 5 ppm from the Schaefer study is:

$$5 \text{ ppm} \times \frac{0.39 \text{ m}^3/\text{kg}/\text{day}}{0.26 \text{ m}^3/\text{kg}/\text{day}} \times \frac{7 \text{ hours}}{24 \text{ hours}} \times \frac{5 \text{ days}}{7 \text{ days}} = 1.56 \text{ ppm}$$

^{c/} Reference concentration is 1/100 of the human equivalent NOEL.

Table 5. Critical No-Observed-Effect Levels and reference concentrations for methyl bromide risk characterization.

| Scenarios | Experimental NOEL | Human Equivalent NOEL ^a | | Reference Concentration ^d | Effects in Animal Studies | Ref ^e |
|-----------------------------|----------------------|------------------------------------|--------------------|--------------------------------------|--|------------------|
| | | Adult ^b | Child ^c | | | |
| Acute | 40 ppm | 21 ppm | na | 210 ppb | Developmental toxicity (pregnant rabbit) | 1* |
| | 103 ppm ^f | 45 ppm | 25 ppm | 250 ppb | Neurotoxicity (dog) | 2 |
| Subchronic 1 week | 20 ppm | 12 ppm | 7 ppm | 120 ppb(adult) 70 ppb (child) | Neurotoxicity (pregnant rabbit) | 3 |
| 6 weeks | 5 ppm | 1.56 ppm | 0.88 ppm | 16 ppb (adult) 9 ppb (child) | Neurotoxicity (dogs) | 4 |
| Chronic | 0.3 ppm (ENEL) | 0.2 ppm | 0.1 ppm | 2 ppb (adult) 1 ppb (child) | Nasal epithelial hyperplasia/ degeneration (rat) | 5* |

^{a/} Experimental NOELs were converted to human equivalents using equations to account for differences in breathing rates and duration of exposures. na= child equivalent NOEL were not calculated because the effects were observed in pregnant animals.

^{b/} The adult equivalent NOELs are appropriate to address worker exposures. They are also used for residential exposures when child equivalent NOELs were not calculated.

^{c/} The child equivalent NOELs are appropriate to address resident exposures (see footnote b).

^{d/} The reference concentration is the ratio of the human equivalent NOEL and a default uncertainty factor of 100 since the NOEL was derived from experimental animal studies.

^{e/} * indicates study was acceptable to DPR according to FIFRA guidelines. References: 1. Breslin *et al.*, 1990; 2. Newton, 1994; 3. Sikov *et al.*, 1981; 4. Schaefer, 2002; 5. Reuzel *et al.*, 1987 and 1991.

^{f/} The NOEL and human equivalents are presented in this Table for comparison purposes only. They are not used for risk characterization since the reference concentration lower than that for developmental toxicity.

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